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Towards a Potential Paradigm Shift for the Clinical Care of Diabetic Patients Requiring Perineural Analgesia: Strategies for Using the Diabetic Rodent Model

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In this issue of *Regional Anesthesia and Pain Medicine*, Kroin et al.¹ take an important step in the evaluation of peripheral nerve block safety in the setting of diabetes, answering the call for focused research on this topic.² To these authors' credit, they meticulously crafted methods in a diabetic rodent model, used detailed staining techniques and precise fiber-counting strategies for histologic analysis, and have come up with fair and reasonable conclusions. In addition, they responsibly addressed concerns during the peer-review process, including the performance of sciatic nerve blocks using two separate techniques (percutaneous nerve stimulator technique and direct visualization with open surgical incision).

The key clinical issue for which this study presents translational potential relates to the pathophysiology of diabetic polyneuropathy (DPN).³ DPN features losses of both myelinated and unmyelinated fibers, with axonal degeneration and decreased myelin remodeling, and loss of Schwann cells. Small-vessel changes in extrinsic (epi- and perineurial) vasculature (affected by adrenergic pharmacology⁴) is more attributed to atherosclerosis than DPN, *per se*.³ Meanwhile, small vessel changes in endoneurial (intrinsic, nutritive⁴) capillaries (i.e., those unaffected by adrenergic pharmacology) involve the thickening of basement membranes. The intrinsic-extrinsic dual blood supply of peripheral nerves⁴ would seem to render diabetic nerves as subject to potential neuronal ischemia and infarction³ (i.e., if vasoconstriction of the extrinsic vessels leads to an insufficient "watershed" for the intrinsic vessels).

It is accepted that many local anesthetics (including lidocaine and ropivacaine) are inherently vasoconstrictive. Additional vasoconstrictive properties of epinephrine on alpha-1 adrenoreceptors (among epinephrine's other potential analgesic properties such as agonist activity of the alpha-2A adrenoreceptor⁴) prolong the clinical duration of local anesthetic nerve blocks. The worsening of neuronal ischemia by local anesthetic nerve blocks with epinephrine is likely due to reduced local anesthetic clearance, as opposed to direct epinephrine toxicity.⁴ These factors should be especially worrisome to clinicians caring for diabetic patients. From the perspective of the diabetic patient, subclinical decrements in nerve function after a nerve block may only be detectable with "before-and-after" electromyography. In rat⁵ and human⁶ ischemic conduction block models (tourniquet inflation, not involving perineural local anesthetics), diabetic nerves were slower to achieve conduction block from anoxia than were non-diabetic nerves, but diabetic nerves were significantly and adversely affected in recovery after reperfusion. Diabetic nerves are at more risk for complications than non-diabetic nerves.

The primary findings in Kroin et al's study¹ of potential translational importance are:

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- i. All of the local anesthetic solutions tested (lidocaine 1% with or without epinephrine or clonidine additives, and ropivacaine 0.5%) produced a longer mean duration of sensory nerve block in diabetic rats *versus* non-diabetic rats;
- ii. Lidocaine 1% (plain) was not toxic to the sciatic nerve in diabetic rat, and none of the treatments were toxic to the sciatic nerve in non-diabetic rat;
- iii. Neither the “clinical” dose of epinephrine (5 mcg/mL), nor a “supraclinical” dose of clonidine (7.5 mcg/mL) *without* local anesthetics were toxic to the diabetic rat sciatic nerve,
- iv. Block duration in diabetic rat correlated (i.e., cannot declare causation) with nerve fiber degeneration.

Longer duration of sensory nerve block in diabetic rats

Point (i) is consistent with recently published findings in this journal by Gebhard et al.⁷, who reported “higher block success rate” for surgical anesthesia in diabetic versus non-diabetic patients undergoing supraclavicular brachial plexus block with mepivacaine. Clinically, the interpretation of block success is initially the onset of surgical anesthesia, followed by block duration (when desired for postoperative analgesia, as in complex same-day orthopedic surgery). In the case of the diabetic rat study, the parameter of “block success” is block duration (since initial block failure in an animal study would lead to study subject exclusion). “Block success” is in quotes in an effort to be cautious regarding our definitions of “success,” especially in the context of a diabetic rat model.

Lidocaine is not toxic to sciatic nerve in diabetic rat

Lidocaine 1%, 100 mcL, does not appear to be neurotoxic to the sciatic nerve of the diabetic rat, and appears to produce effective short-term sensory anesthesia and motor block. This dose and concentration of lidocaine is likely safe for peripheral nerve blocks in diabetic patients; it has not caused significant problems in this patient population to date. We cannot determine from this or any other study to date that diabetic blocks last longer because of toxicity, reduced clearance, or other factors. Despite appropriate concerns, there is little evidence from wide clinical experience or published surveys that diabetic patients are more prone to injury after peripheral nerve block; such surveys and studies are otherwise pending. That diabetic nerve is more prone to any injury is unequivocal, but that diabetic nerves in patients are more prone to injuries from nerve blocks still requires study. We cannot assume diabetic perineural safety in the absence of systematic prospective (or even retrospective) outcome surveys, and/or more detailed methods. Understanding that at constant volumes, nerve damage is directly related to local anesthetic concentration, a dose-response study addressing lidocaine 1% versus 1.5% (for example) in diabetic patients is warranted.

Epinephrine and clonidine were not anesthetic or analgesic in rat diabetic nerve when used as monotherapy

Point (iii) first addresses epinephrine 5 mcg/mL, 100 mcL, which (as monotherapy) appears to be neither anesthetic nor analgesic in rat diabetic nerve. There is likely no detectable value of epinephrine perineural analgesic monotherapy in the setting of diabetes (or otherwise) in rat; any alpha-2 mediated analgesic agonist effect appears to only have 10 min duration.⁸ In human, the presence of epinephrine showed no apparent independent pharmacodynamic analgesic effect when combined with lidocaine.⁹

However, there are no apparent studies of low-dose epinephrine in diabetic rat in combination with perineural analgesics (other than local anesthetics), these may be of potential clinical value

in augmenting analgesia. This was first illustrated clinically by Candido et al.^{10,11} who demonstrated a remarkable increase in brachial plexus block duration (17 hr and 22 hr in 2 separate studies) when buprenorphine was combined with mepivacaine, tetracaine, and epinephrine (5 mcg/mL). One cannot rule out that a buprenorphine-epinephrine interaction may have contributed to such a remarkable duration, and this combination should be evaluated further in rodent models. This similar concept of potential epinephrine interactions with novel perineural analgesics can be further speculated based on the recent clinical study by Vieira et al. (2009)¹², in which dexamethasone 8 mg was added to bupivacaine 0.5%, clonidine 75 mcg, and epinephrine 5 mcg/mL. This combination clinical study (with no laboratory model precedent) yielded a median 24 hr nerve block with dexamethasone and 14 hr without dexamethasone. One cannot rule out a clonidine-epinephrine interaction, or a clonidine-epinephrine-dexamethasone interaction, as possible contributors to this remarkable difference in nerve block duration. In either case, if these epinephrine effects can be produced in rat model, it will be important to distinguish whether the effects are related to reduced focal drug clearance, or type-2 adrenoreceptor agonist analgesic effect, or both.

Continuing with point (iii), clonidine 7.5 mcg/mL, 100 mcL appears to be neither anesthetic nor analgesic in rat diabetic nerve. Kroin et al.¹ justifiably chose 7.5 mcg/mL for this model since this dose has been shown to prolong nerve block duration in rat, whereas lower doses have not. This dose, extrapolated to a 20 mL injection in a 100 kg patient, would translate to 1.5 mcg/kg, which in non-diabetics would commonly lead to hypotension, bradycardia, and sedation. Clinically, a perineural dose in the range of 0.5 mcg/kg would more likely be considered in the setting of diabetes, as to reduce potential hemodynamic side effects of clonidine in the setting of associated autonomic dysfunction.

There is likely no value of clonidine perineural analgesic monotherapy in the setting of clinical diabetes, based on the present rat study and also based on the clinical study of Sia et al. (1999) which applied 150 mcg clonidine to the brachial plexus in non-diabetic patients (and showing no analgesic benefit when compared with saline placebo).¹³ Mechanistically, Kroin et al. (2004) previously reported that the mechanism of the enhancement of perineural analgesia by clonidine with lidocaine is not via alpha-2 adrenoreceptor agonist activity, but rather via hyperpolarization-activated (I_h) current.¹⁴ Later studies on rat dorsal root ganglia added to this concept by finding that clonidine (monotherapy) has action potential-dependent direct effects on sodium channels.¹⁵ In either case, it is important to evaluate clinically relevant doses of clonidine not only with respect to the prolonging of local anesthetic block duration, but also in the contexts of (i) potentiation of other perineural analgesics; and (ii) potential perineural protection and anti-inflammatory effect (in the non-diabetic rodent model *in vivo*).^{16–19} A future study of sciatic nerve blocks in diabetic rats containing 1% plain lidocaine versus 1% lidocaine with clonidine 0.5 mcg/mL should be performed to investigate the potential perineural protective effects of clonidine, at least with respect to histologic outcomes. Likewise, we should continue to evaluate the entire dose-response spectrum regarding all local anesthetics (in doses as low as possible) combined with clinically relevant doses of clonidine in the diabetic rodent model.

In the absence of neuronal cytotoxicity safety data for these elegant perineural combinations, my laboratory has cultured primary sensory neurons from Sprague-Dawley rat and exposed them for 24 hr to combined clonidine (1 mcg/mL), buprenorphine (3 mcg/mL) and dexamethasone (66.6 mcg/mL) (without local anesthetics, without epinephrine). In these studies, there was no difference in toxicity when compared with an isomolar choline control solution (unpublished data, manuscript in preparation). This translational bench study was inspired by our group's case report of motor-sparing perineural catheter analgesia with clonidine-buprenorphine (and no local anesthetic).²⁰

Block duration in diabetic rat correlated (i.e., cannot declare causation) with nerve fiber degeneration

Point (iv) addresses the findings that nerve block duration was correlated with fiber degeneration. In rat diabetic sciatic nerve in the present study, ropivacaine 0.5% (plain) caused degeneration. The addition of epinephrine and clonidine to 1% lidocaine in rat diabetic nerve prolonged the duration of anesthesia, again correlating with nerve fiber degeneration. However, the clonidine dose used was higher than that likely used clinically (as described above). Additionally (as the authors appropriately commented), this study¹ was not designed as a dose-response study of clonidine in a fixed concentration of lidocaine with respect to nerve block duration and nerve fiber degeneration in diabetic rat. Likewise, this was not a dose-response study of epinephrine in a fixed concentration of lidocaine. If a practitioner wishes to use epinephrine as an intravascular marker in a diabetic patient, caution would be advised by considering a lower epinephrine concentration (e.g., 2.5 mcg/mL), and using the lowest total volume of epinephrine containing injectate possible (e.g., 5–10 mL as a “test dose,” as opposed to 20 mL or more).

In a recent translational vignette published in this journal, it was declared that preliminary study of novel perineural analgesics in diabetic animal models should answer several key questions.³ Specifically (paraphrased almost verbatim), are such perineural additives alone or in combination (i) antinociceptive, (ii) more motor sparing than are local anesthetics, (iii) reversible in their antinociceptive and motor-proprioceptive block effects, and (iv) histologically safe upon microscopic examination of harvested nerve?³ If any such adjuvants do not meet these criteria as monotherapy and/or as combination (with each other and/or with local anesthetics), then it would be illogical to further evaluate the mechanism of a perineural adjuvant that has already been tested in humans in the absence of animal safety evidence. Based on the current data of Kroin et al.¹ (in addition to points (i) through (iv) above), we can conclude the following using these criteria.

(a) Epinephrine and/or clonidine remain viable candidates for perineural study in diabetic and non-diabetic animals, in the context of combinations of adjuvants *without* local anesthetics (e.g., buprenorphine, clonidine, tramadol, etc.) aiming to achieve perineural analgesia without motor block. *Testing perineural dexamethasone in diabetic patients remains ill-advised at this time*; diabetic patients are immunosuppressed, and dexamethasone is immunosuppressive. However, testing dexamethasone in diabetic and non-diabetic animals may reveal important concepts (or cautions) regarding nerve blocks in diabetic and non-diabetic patients.

(b) How we interpret the outcomes of a streptozotocin-induced diabetic (STZ-diabetic) rat model with sciatic neuropathy should not involve inappropriate conservatism. STZ-diabetes in rat does not resemble “Type I” or “Type II” diabetes in humans; there is no diabetic rat model that closely resembles that of the human condition.³ First, our goal as practitioners should be to better estimate the risk of permanent nerve damage specifically in the setting of nerve blocks in diabetic patients. If long-term risk (complications six months and beyond) in non-diabetic patients lie in the range of 1:3000 and 1:10,000^{21,22}, then let us assume that the risk of long-term neuropathy in diabetics is 1:1000 (i.e., assume 3–10 times more risk vs non-diabetics). As Kroin et al.¹ astutely observed, diabetic rodent models should guide us toward doses that are risk-free in rats, which would hopefully reduce the long-term neuropathic risks in diabetics from our theoretical 1:1000 back to 1:10,000. Perhaps avoiding local anesthetics altogether may be the answer, and future studies using combinations of other perineural analgesics are warranted, from a public health standpoint.

It is obvious from this study¹ that duration of perineural analgesia in STZ-diabetic rat is correlated with nerve fiber degeneration. It is also obvious that local anesthetics are the “driver”

of this nerve fiber degeneration, with duration only being *correlated* with the extent of damage. We *cannot* extrapolate block duration as being a driver of neuropathy-nerve damage in diabetic patients. Indeed, the temporary cellular disruption shown in this study occurs with all local anesthetics, and is not specific to the context of diabetes. We can and should use the STZ-diabetic rat model to re-evaluate our current practices for our diabetic patients. We cannot overlook the clinical importance of nerve block analgesia in an effort to minimize systemic opioid requirements (and potential opioid-induced hyperalgesia²³), unplanned hospital admissions/readmissions^{24,25}, and rebound pain after a local anesthetic nerve block resolves.²⁶ A general anesthetic (to avoid complications associated with peripheral nerve blocks) is not exactly a risk-free alternative for our diabetic patients. This study¹ indeed makes an important step to further justify the pursuit of perineural analgesia without using local anesthetics as the centerpiece.

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